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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/376,604 | 08/18/1999 | RAGUPATHY MADIYALAKAN | 107823.129 | 6693 |

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|---|---|
| NICKOL, GARY B | |
| ART UNIT | PAPER NUMBER |
| 1642 | 26 |

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/376,604 | MADIYALAKAN ET AL. | |
| | Examiner | Art Unit | |
| | Gary B. Nickol Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *113,115-135,137-144,170-175 and 177-234* is/are pending in the application.

4a) Of the above claim(s) *210-234* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113,115-135,137-144,170-175 and 177-209* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Response to Amendment***

The Amendment filed December 23, 2002 (Paper No. 25) in response to the Letter mailed December 14, 2002 is acknowledged and has been entered. This office action is in response to the amendment filed January 4, 2002 (Paper No. 15).

Claim 176 was cancelled. Claims 210-234 were added.

Claims 113, 115-135, 137-144, 170-175, 177-234 are pending.

Claims 210- 234 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 113, 115-135, 137-144, 170-175, 177-209 are currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

***Election/Restrictions***

Newly submitted claims 210-234 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 210-234 are broadly drawn to administering a composition comprising an antigen and a binding agent whereas the elected claims are solely drawn to administering a composition comprising a binding agent which is non-radiolabeled. Applicant's originally elected to prosecute the invention of Group I, drawn to a method of inducing an immune response using a non-radiolabeled binding agent corresponding to original claims 113, 115-135, and 137-144 (Paper No. 7).

Since the administered compositions of claims 210-234 are independent from the elected invention and since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 210-234 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

### *Terminal Disclaimer*

The terminal disclaimer filed on 1-04-02 (Paper No. 18) disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 6,241,985 has been reviewed and is accepted. The terminal disclaimer has been recorded.

## NEW REJECTIONS/OBJECTIONS

### *Specification*

The specification is objected for reciting "lose" on page 18, line 12 because it appears to be a grammatical error.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 113, 126-127, 174, 188-189 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 113, 126-127, 141, 170, 174, 188-189, 197, 201, and 206 are vague because the base claims (113,135, 174, and 201) define the binding agents as those that are non-radiolabeled binding agents. Thus, these agents are interpreted as binding agents which have *not* been exposed to radiation. However, dependent claims 126-127 and 188-189 further characterize the binding agents as having been exposed to radiation. Further, claims 141, 170, 197, and 206 encompass binding reagents which have been exposed to radiation in that they are drawn to **any** imaging reagent which includes *radioisotopes*. Thus, the claims are apparently contradictory in nature and do not particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 113, 122-125, 135, 140, 174, 184-187, 201, and 205 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or

guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to inducing a therapeutic host immune response against a multi-epitopic in-vivo antigen (one that does not elicit an effective host immune response) comprising contacting a multi-epitopic antigen present in a host's serum with a composition comprising a binding agent that specifically binds to a first epitope on the antigen, the binding agent present in a composition being non-radiolabeled, and allowing the binding agent to form a binding agent/antigen pair, whereby an effective host immune response is elicited against a second epitope on the antigen in the binding agent/antigen pair wherein the binding agent is a murine monoclonal antibody such as B43.13 wherein the antibody does not induce isotypic HAMA-induced toxicity in the host.

The claims are not enabled because the there is insufficient guidance and objective evidence to predictably enable one of ordinary skill in the art to administer murine monoclonal antibodies (such as B43.13) in the absence of HAMA-induced toxicity in a **human** host. (Applicant is advised that base claims 113, 135, 174, and 201 are interpreted as encompassing a human host.)

The specification teaches (page 19) that in certain embodiments the antibody does **not** induce antibody-mediated toxicity, e.g. isotypic induced HAMA toxicity in the host. Thus, in its broadest reasonable interpretation, it appears that the specification is teaching that the murine monoclonal antibody B43.13 will NOT provoke a HAMA reaction. However, one cannot extrapolate the teachings of the specification to that which is claimed because the specification

also appears to teach that HAMA reactions *were* observed upon injection of B43.13. For example, the specification teaches (page 49), that when patients received more than one injection and patients developed *high* amounts of human anti-mouse antibodies (HAMA), the antibody showed rapid clearance to liver and spleen. Furthermore, Madiyalakan *et al.* (Hybridoma, Vol. 14, Number 2, 1995, pages 199-203, IDS) teach that a large majority of patients developed isotypic HAMA (page 201, 2nd column; and Figure 3) upon injection of mAB B43.13.

Thus, because the claims are specifically drawn to the administration of murine monoclonal antibodies that do not elicit an isotypic HAMA reaction, and because it appears that such reactions do take place when said antibodies are administered to humans, it appears that undue experimentation would be required to practice the invention as claimed.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 113, 115-123, 128, 131-135, 137-139, 141-144, 170-175, 177-185, 190, 193-204, 206-209 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,997,315 (Chatterjee *et al.*, December, 28, 1994).

US Patent No. 5,997,315 teaches methods for inducing therapeutic host immune responses against a multi-epitopic in-vivo antigen that does not elicit an effective host immune response comprising contacting a multi-epitopic antigen present in a host's serum with a composition comprising a binding agent that specifically binds to a first epitope on the antigen, the binding agent present in the composition being non-radiolabeled, and allowing the binding agent to form a binding agent/antigen pair, whereby an effective host immune response is elicited against a second epitope on the antigen in the binding agent/antigen pair (See columns 1, line 63-66 to column 2, lines 1-65; column 12, line 42- the antibody may be administered in an unmodified form; or column 31, line 35- the administered antibody is non-radiolabeled). The patent further teaches that the host immune response may comprise a cellular or humoral immune response (column 7, line 14) and that the multi-epitopic antigen is a soluble tumor-associated antigen associated with a human disease or condition wherein the human disease or condition is cancer wherein the binding agent is a murine monoclonal antibody (column 6, lines 64+; column 10, lines 58-62). The patent further teaches that the antigen is soluble "circulating" antigen (column 2, line 52) where inherently the antigen is contacted with a sufficient amount of antibody to present all the circulating antigen to the immune system. Typical dosage of the binding agent ranges from 0.1mg to about 20mg which encompasses 0.1μg to 2mg, 1ug to 2mg,

or 1μg to 200μg (i.e. 0.2 mg) per kg of body weight in the host (column 11, lines 40+). The patent further teaches that one way an immune response is elicited may be that the binding agent combining site may present a region that partly resembles an epitope in CEA, in the context of other epitopes which renders it more immunogenic. The later broadly reads on allowing the binding agent to form a binding agent/antigen pair which presents other epitopes on the antigen to the host's immune system (column 7, line 16). The patent further teaches that the binding agent may be administered with a variety of adjutants, carriers, imaging reagents via immunologically suitable routes (column 9, lines 29+; column 11, lines 35+ & 55+ to column 12).

Claims 113, 115-123, 125-126, 129-135, 137-139, 141-144, 170-185, 187-188, 191-204, and 206-209 are rejected under 35 USC 102(b) as being anticipated by Madiyalakan *et al.* (Hybridoma, Vol. 14, No. 2, pages 199-203, 1995, IDS) for the reasons of record in Paper No. 14.

Applicants argue (Paper No. 15, page 6) that the independent claims require the use of a non-radiolabeled binding agent in the claimed method, and that in contrast, the binding agent administered in the method of Madiyalakan *et al.* is a radiolabeled B43.13 antibody. This argument has been considered but is not found persuasive due to the apparent discrepancy in the claimed subject matter with regards to exposure to radiation. See 112, 2nd paragraph rejection above.

**All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.** (Note: due to large number of pending claims, applicant is requested to submit a clean version of all pending claims with any amendment in response to this action.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
March 25, 2003